Infection (2013) 41:811–820
DOI 10.1007/s15010-013-0460-9

CLINICAL AND EPIDEMIOLOGICAL STUDY

Development of acute kidney injury during continuous infusion of vancomycin in septic patients

S. Cianferoni · A. Devigili · E. Ocampos-Martinez · L. Penaccini · S. Scolletta · A. Abdelhadii · D. De Backer · M. Beumier · F. Jacobs · J.-L. Vincent · F. S. Taccone

Received: 23 December 2012 / Accepted: 28 March 2013 / Published online: 10 April 2013

Abstract
Purpose Few data are available on the occurrence of renal failure during continuous infusion of vancomycin in critically ill patients.
Methods We reviewed the data of all patients admitted to the intensive care unit (ICU) between January 2008 and December 2009 in whom vancomycin was given as a continuous infusion for more than 48 h in the absence of renal replacement therapy. We collected data on the doses of vancomycin and blood concentrations during therapy. Acute kidney injury (AKI) was defined as a daily urine output <0.5 ml/kg/h and/or an increase in the serum creatinine of ≥0.3 mg/dl from baseline levels during vancomycin therapy or within 72 h after its discontinuation. Multivariable logistic regression analysis was performed to identify predictors of AKI.
Results Of 207 patients who met the inclusion criteria, 50 (24 %) developed AKI. These patients were more severely ill, had lower creatinine clearance at admission, were more frequently exposed to other nephrotoxic agents, had a longer duration of therapy, and had higher concentrations of vancomycin during the first 3 days of treatment (C_{mean}). The C_{mean} was independently associated with early AKI (within 48 h from the onset of therapy) and the duration of vancomycin administration with late AKI.
Conclusions AKI occurred in almost 25 % of critically ill patients treated with a continuous infusion of vancomycin. Vancomycin concentrations and duration of therapy were the strongest variables associated with the development of early and late AKI during therapy, respectively.

Keywords Vancomycin · Dose regimen · Renal failure · Continuous infusion · Critically ill

S. Cianferoni · A. Devigili · E. Ocampos-Martinez · L. Penaccini · S. Scolletta · A. Abdelhadii · D. De Backer · M. Beumier · J.-L. Vincent · F. S. Taccone (✉)
Department of Intensive Care, Hôpital Erasme, Université Libre de Bruxelles (ULB), Route de Lennik, 808, 1070 Brussels, Belgium
e-mail: ftaccone@ulb.ac.be

F. Jacobs
Department of Infectious Diseases, Hôpital Erasme, Université Libre de Bruxelles (ULB), Route de Lennik, 808, 1070 Brussels, Belgium

Introduction

Severe Gram-positive bacteria infections, especially if due to methicillin-resistant *Staphylococcus aureus* (MRSA), represent a major nosocomial problem associated with high morbidity and mortality [1]. MRSA infections are responsible for more than one tenth of all cases of septic shock [2] and can be an independent determinant of in-hospital mortality among critically ill patients [3]. Vancomycin remains one of the first antibiotic choices for the treatment of severe MRSA infections [4]. However, several studies suggested that standard vancomycin regimens were inadequate to efficiently treat more resistant strains of MRSA, especially those with a minimum inhibitory concentration (MIC) for the drug above 1 μg/ml [5]. Recent recommendations for intermittent infusion have, thus, highlighted the importance of achieving serum trough vancomycin concentrations of 15–20 μg/ml when treating MRSA infections in critically ill patients [4].

A key concern during vancomycin therapy is the development of acute kidney injury (AKI), with an incidence as high as 40 % in some studies [6, 7]. Several retrospective reports have suggested that the risk of AKI is

increased when initial vancomycin doses exceed 4 g/day or when drug concentrations exceed 15 μg/ml [8–11]. A recent randomized clinical trial also showed that vancomycin was associated with a greater incidence of AKI when compared to linezolid in the treatment of MRSA pneumonia [12]. Nevertheless, these studies did not specifically focus on critically ill patients, in whom the pharmacokinetics of vancomycin can be significantly altered, resulting in inadequate drug concentrations [13], and who are at high risk of developing AKI [14]. In this setting, one effective approach to maximizing the antimicrobial activity of vancomycin is to use a continuous infusion [15]. Although this approach has not been shown to improve clinical efficacy in MRSA infections when compared to standard intermittent regimens [16], continuous infusion may achieve therapeutic vancomycin concentrations more rapidly, may facilitate dose adjustment, and may reduce variability in drug levels [16]. A continuous infusion may also decrease the risk of AKI when compared to standard repeated infusions [17], although few data are available on the potential nephrotoxicity of continuous vancomycin infusions in critically ill patients [18]. The objectives of this study were, therefore, to evaluate the incidence of AKI during a continuous infusion of vancomycin in septic patients and to identify the risk factors and time course (early vs. late) of the development of AKI in this population, as well as the long-term consequences of continuous vancomycin infusions on renal function.

Methods

Patients and data collection

We reviewed a database of adult (>18 years of age) patients who were treated with a continuous infusion of vancomycin, either as monotherapy or combined with other antimicrobials, in our multidisciplinary Department of Intensive Care, over a two-year period (from 1st of January 2008 to the 31st of December 2009). Patients were included in the analysis if they: (a) had a diagnosis of sepsis, according to standard criteria [19]; (b) had received vancomycin therapy for more than 48 h; (c) had undergone daily drug monitoring; (d) had a total body weight (TBW) noted in the data file; (e) were not being treated with continuous renal replacement therapy (CRRT) or conventional hemodialysis (HD) at the time of initiation of vancomycin therapy. We excluded patients who had received vancomycin within the week prior to the present episode, those with end-stage renal failure chronically treated with HD, and those with missing data on serum creatinine (sCr), urine output, and/or concomitant administration of nephrotoxic agents. The study was approved by the Ethics Committee, which waived the need for informed consent in view of its retrospective nature.

We collected demographics, pre-existing chronic diseases, admission diagnosis, biological, and microbiological data for all patients. The severity of illness is assessed routinely on admission using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [20] and the Sequential Organ Failure Assessment (SOFA) [21] score. SOFA scores are also routinely calculated daily during the intensive care unit (ICU) stay. sCr levels at the start of and during vancomycin therapy were recorded, as was the creatinine clearance (CrCl) on the first day of therapy, calculated from the 24-h urine collection and normalized to the body surface area (BSA). Treatment with vasoactive drugs and mechanical ventilation during vancomycin therapy was recorded, as was the length of ICU stay and overall ICU mortality.

Vancomycin therapy

In our department, continuous infusion is the standard mode of administration for vancomycin for ICU patients when treating suspected or documented infections due to MRSA or other Gram-positive bacteria. Serum concentrations of vancomycin were determined by particle enhanced turbidimetric inhibition immunoassay (Dimension Xpand, Siemens Healthcare Diagnostics, Newark, DE). The limit of quantification and total imprecision of the assay were 0.8 mg/ml and <5 %, respectively. Blood samples (3 ml) were taken every day at 8 a.m. and sent immediately to the central laboratory. The exact sampling time was recorded by the nursing staff in the patient data monitoring system (Picis Critical Care Manager, Picis Inc., Wakefield, MA).

Vancomycin was administered as a 15 mg/kg loading dose over 60–90 min (maximum rate: 1 g/h), followed by a 20–30 mg/kg daily continuous infusion calculated using TBW, according to the CrCl, as previously described [11]. The aim was to reach serum concentrations between 20 and 30 μg/ml. Thus, if the serum vancomycin concentration was less than 20 μg/ml, an additional bolus of 500 mg was given, followed by an increase in the daily dose by 500–1,000 mg. If the concentration was greater than 30 μg/ml, the continuous infusion was discontinued for at least 4 h and the daily dose reduced by 500–1,000 mg per day.

Vancomycin concentrations were routinely measured every day at 8 a.m. in all patients receiving vancomycin continuous infusion. We specifically considered: drug concentration on day 1; mean vancomycin concentration over the first 3 days of therapy (C_{mean}, or the first 2 days of therapy if the drug was administered for only 48 h); and maximal drug concentrations over the entire vancomycin therapy (C_{max}).

Definitions

The development of AKI was defined as a daily urine output <0.5 ml/kg/h and/or an increase in the sCr level of at least 0.3 mg/dl or a 1.5–2 times increase from baseline (i.e., the first day of vancomycin therapy), whichever was greater, on at least two consecutive days during and in the 72 h after vancomycin discontinuation. We considered only the daily urine output, as this measure may be less influenced by the effects of specific therapies, such as volume loading and diuretic administration, compared to partial urine outputs over 6–12 h. We also recorded any potentially nephrotoxic agents which were administered concomitantly, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, amphotericin B, colistin, and immunosuppressant agents (e.g., calcineurin inhibitors, such as ciclosporin and tacrolimus). Exposure to intravenous contrast media was considered to be potentially nephrotoxic only if given within 5 days before the start of vancomycin therapy and/or during drug infusion.

AKI was considered as 'early' if it developed within the first 2 days of therapy and 'late' if it occurred thereafter. The development of severe AKI was defined as the need for CRRT or HD during vancomycin therapy and within 3 days after drug discontinuation. To evaluate the long-term effects on renal function, we recorded the need for CRRT/HD and sCr concentrations at 1 month (±7 days) after the initiation of therapy.

Statistical analysis

Statistical analyses were performed using the SPSS 18.0 for Windows NT software package (SPSS Inc., 2004, Chicago, IL). Descriptive statistics were computed for all study variables. A Kolmogorov–Smirnov test was used, and histograms and normal–quantile plots were examined to verify the normality of distribution of continuous variables. Discrete variables were expressed as counts (percentage) and continuous variables as mean ± standard deviation (SD) or median [25th–75th percentiles]. Demographics and clinical differences between groups (AKI vs. no AKI; early AKI vs. late AKI) were assessed using a Chi-square test, Fisher's exact test, Student's *t*-test, or Mann–Whitney *U*-test, as appropriate. Multivariable logistic regression analysis with AKI development during vancomycin therapy as the dependent variable was performed in all patients; only variables associated with a higher risk of inadequate concentrations ($p < 0.2$) on a univariate basis were introduced in the multivariate model. Collinearity between variables was excluded prior to modeling; the influence that individual observations could exert on the coefficients was also evaluated. Odds ratios (ORs) with 95 % confidence intervals (CIs) were computed. Variables considered in the analysis were demographic variables, co-morbidities, APACHE II score on admission, SOFA scores on days 1 and 2 of therapy, type of admission (medical or surgical), source of infection, mechanical ventilation, administration of vasopressor agents, vancomycin doses (loading and daily dose; mean dose over the first 3 days of therapy, $Dose_{mean}$), vancomycin concentrations (on day 1, C_{mean} and C_{max}), and CrCl. The same analysis was then performed for early and late AKI, separately. The discriminative ability of variables identified by multivariate analysis to predict the development of AKI was evaluated using receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUC). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also computed. A p-value < 0.05 was considered as being statistically significant.

Results

During the study period, 207 patients met the inclusion criteria (Fig. 1); their characteristics are shown in Table 1. The lung ($n = 103$, 50 %) was the most common source of infection, followed by the abdomen ($n = 44$, 21 %) and the urine ($n = 27$, 13 %). Gram-positive organisms were identified in 112 patients (65 %), including methicillin-sensitive *S. aureus* (MSSA) in 30 (27 %), MRSA in 22 (20 %), coagulase-negative *Staphylococcus* ssp. in 30 (27 %), *Enterococcus* ssp. in 21 (19 %), and others in 9 (8 %).

Fifty patients (24 %) developed AKI during vancomycin therapy. These patients more frequently had diabetes and cirrhosis and were more severely ill than the other patients,

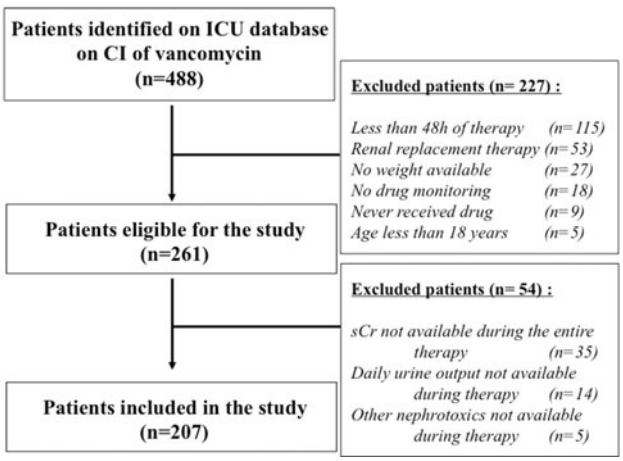

Fig. 1 Flow chart of the study. *sCr* serum creatinine

Table 1 Characteristics of the study population, with regard to the development of acute kidney injury (AKI) during vancomycin therapy ($n = 207$, no missing values)

	All patients ($n = 207$)	No AKI ($n = 157$)	AKI ($n = 50$)	Early AKI ($n = 28$)	Late AKI ($n = 22$)
Age (years)	60 ± 15	60 ± 15	61 ± 14	62 ± 13	59 ± 15
Men/women	130/77	98/59	32/18	18/10	13/9
BMI (kg/m^2)	25 [22–29]	25 [22–28]	26 [23–29]	27 [25–29]	26 [22–30]
COPD/asthma, *n* (%)	51 (25)	40 (25)	11 (22)	6 (21)	5 (22)
Hypertension, *n* (%)	78 (38)	64 (41)	14 (28)[b]	8 (29)[b]	6 (27)[b]
Cardiopathy, *n* (%)	56 (27)	39 (25)	17 (34)	12 (43)	5 (22)
Diabetes, *n* (%)	53 (26)	34 (22)	19 (38)[a]	9 (32)[a]	10 (45)[a]
Cancer, *n* (%)	64 (31)	53 (34)	11 (22)[b]	6 (21)[b]	5 (22)[b]
Liver cirrhosis, *n* (%)	17 (8)	8 (5)	9 (18)[a]	3 (11)[a]	6 (27)[a]
TVD, *n* (%)	12 (6)	5 (3)	7 (14)[a]	4 (14)[a]	3 (13)[a]
Smoking, *n* (%)	40 (19)	33 (21)	7 (14)	7 (25)	0 (0)[a,c]
Alcohol, *n* (%)	35 (17)	26 (16)	9 (18)	5 (18)	4 (18)
Medical admission, *n* (%)	123 (59)	92 (59)	31 (62)	17 (60)	14 (63)
APACHE II score on admission	20 [16–27]	19 [15–25]	24 [18–30][a]	24 [19–29][a]	21 [16–29][c]
SOFA II score on admission	8 [5–11]	7 [3–10]	9 [4–12][a]	10 [6–13][a]	8 [6–11][b,c]
Bacteremia, *n* (%)	37 (18)	26 (16)	11 (22)	9 (32)[a]	2 (9)[c]
Days of vancomycin therapy	4 [3–6]	4 [3–6]	5 [3–9][a]	5 [3–7][b]	5 [4–9][b]
Loading dose (mg)	1,000 [1,000–1,500]	1,000 [1,000–1,500]	1,000 [1,000–1,500]	1,000 [1,000–1,500]	1,000 [1,000–1,500]
Mean dose days 1–3 (mg)	2,000 [1,697–2,500]	2,000 [1,800–2,642]	1,940 [1,431–2,212][a]	1,747 [1,206–2,000][a]	2,050 [1,714–2,691]
Total dose (mg)	8,100 [6,000–13,500]	9,450 [7,000–14,000]	11,500 [7,525–16,875][b]	9,500 [7,000–12,500]	14,750 [10,250–19,750][a,c]
Maximum daily dose (mg)	2,000 [2,000–3,000]	2,000 [2,000–3,000]	2,000 [2,000–2,937]	2,000 [1,725–2,000]	2,500 [2,000–3,000]
Vancomycin levels on day 1 (μg/ml)	19.7 ± 8.5	18.7 ± 7.0	22.5 ± 9.6[a]	24.5 ± 7.8[a]	20.2 ± 11.1[b,c]
C_{mean} (μg/ml)	22.3 ± 7.0	21.2 ± 6.8	25.8 ± 6.6[a]	27.2 ± 5.1[a]	24.1 ± 7.8[b,c]
C_{max} (μg/ml)	27.5 ± 9.1	26.6 ± 8.2	34.3 ± 8.1[a]	33.5 ± 7.0[a]	35.3 ± 9.1[a]
CrCl (ml/min 1.73 m^2)	68 [31–108]	72 [35–117]	44 [26–88][a]	36 [20–49][a]	85 [38–101][c]
Vasopressor therapy, *n* (%)	69 (33)	56 (35)	13 (26)	8 (28)	5 (22)[b]
Inotropic therapy, *n* (%)	27 (17)	16 (10)	9 (18)	7 (25)	2 (9)
Mechanical ventilation, *n* (%)	142 (69)	106 (68)	36 (72)	21 (75)	15 (68)
Number of nephrotoxics	1 [1–2]	1 [0–2]	2 [1–2][a]	1 [1–2]	2 [1–2]
At least one nephrotoxic, *n* (%)	154 (74)	108 (69)	46 (92)[a]	26 (93)[a]	20 (91)[a]
Diuretics	76 (37)	51 (32)	25 (50)[a]	13 (46)[a]	12 (55)[a]
Contrast medium	47 (22)	36 (23)	11 (22)	7 (25)	4 (19)
Aminoglycosides	17 (8)	15 (7)	2 (4)	1 (4)	1 (5)
ACEIs/ARBs	32 (15)	21 (13)	11 (22)	6 (21)	5 (23)
Others	16 (8)	12 (8)	4 (8)	3 (11)	1 (5)
ICU stay (days)	10 [6–18]	10 [5–18]	12 [8–21][a]	11 [8–19][a]	12 [8–19][a]
ICU mortality, *n* (%)	48 (23)	28 (18)	20 (40)[a]	13 (46)[a]	7 (32)[a]

COPD chronic obstructive pulmonary disease, *TVD* thromboembolic venous disease, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *ICU* intensive care unit, C_{mean} mean vancomycin concentration over the first 3 days of therapy, C_{max} maximal drug concentrations over the study period

[a] $p < 0.05$ and [b] $p < 0.02$ versus no-AKI; [c] $p < 0.05$ versus early AKI patients

as shown by higher APACHE II and SOFA scores on admission (Table 1). In addition, patients developing AKI were more frequently exposed to other concomitant nephrotoxics and had lower CrCl values on the first day of therapy than those who did not develop AKI. Finally, patients who developed AKI had a longer duration of therapy, higher vancomycin concentrations on day 1, and higher C_{mean} values than those who did not develop AKI. AKI developed in 2/34 (6 %) patients with $C_{mean} < 15$ µg/ml, in 5/47 (11 %) patients with C_{mean} 15–20 µg/ml, in 18/60 (30 %) patients with C_{mean} 20–25 µg/ml, in 15/39 (38 %) patients with C_{mean} 25–30 µg/ml, and in 10/27 (37 %) patients with $C_{mean} > 30$ µg/ml (Fig. 2). Patients with AKI had a longer ICU stay and higher mortality rate (40 vs. 18 %) than the other patients.

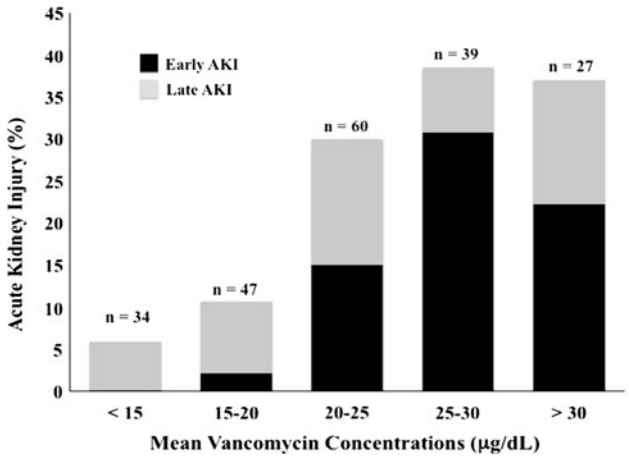

Fig. 2 Proportion of patients developing early and late acute kidney injury (AKI) during vancomycin therapy, according to different ranges of mean vancomycin concentrations during the first 3 days of therapy

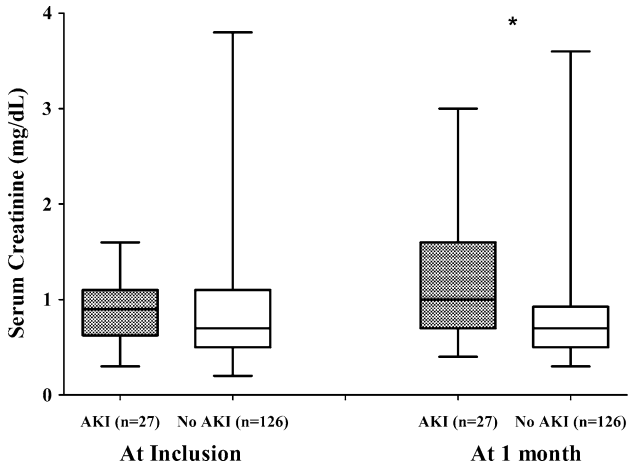

Fig. 3 Serum creatinine (sCr) concentrations at 1 month after the onset of therapy between patients with acute kidney injury (AKI) during vancomycin therapy and those without AKI (*$p = 0.04$)

AKI developed early in 28 patients (56 %) and late in 22 (44 %). Patients with early AKI had higher APACHE II and SOFA scores on admission, higher vancomycin concentrations on day 1, and higher C_{mean} values, as well as lower CrCl values on admission; they also received less vancomycin than those developing late AKI (Table 1). Among the patients developing early AKI, the C_{mean} values were above 25 µg/ml in 18 (64 %), compared to 7 patients (31 %) among those with late AKI ($p = 0.02$; Fig. 2).

Nine patients (18 %) with AKI required CRRT/HD during vancomycin therapy, whereas only 3 patients (2 %) without AKI during vancomycin therapy eventually needed CRRT/HD (9, 11, and 13 days after vancomycin discontinuation, respectively) ($p < 0.01$). Among the survivors ($n = 153$), those who developed AKI ($n = 30$) had a higher sCr at 1 month after the onset of therapy than those without AKI, despite a similar sCr on admission (Fig. 3). Among the nine patients with AKI who required CRRT/HD, five died and one still needed CRRT/HD at 1 month after therapy.

In the multivariable logistic regression analysis, the duration of vancomycin therapy and C_{mean} were independently associated with the occurrence of AKI (Table 2). The AUC to predict the development of AKI was 0.70 (95 % CI, 0.62–0.77) for C_{mean} and 0.71 (95 % CI, 0.63–0.78) for the combination of C_{mean} and duration of therapy (Fig. 4). A $C_{mean} > 30$ µg/ml enabled the prediction of AKI during vancomycin therapy with a sensitivity of 22 %, a specificity of 90 %, a PPV of 40 %, and an NPV of 79 %. Particularly, the effects of different thresholds of combined C_{mean} and duration of therapy on the occurrence of AKI are shown in Fig. 5. In addition, high C_{mean} and low $Dose_{mean}$, as well as bacteremia, were independently

Table 2 Multivariable logistic regression analysis for the development of acute kidney injury (AKI) during continuous infusion of vancomycin ($n = 207$, no missing values)

Variable	Multivariable analysis	
	p-Value	OR (95 % CI)
AKI		
C_{mean} (µg/ml)	<0.001	1.1 (1.04–1.15)
Duration of therapy (days)	0.049	1.12 (1.01–1.25)
Early AKI		
Bacteremia	0.008	1.76 (1.32–1.93)
C_{mean} (µg/ml)	<0.001	1.12 (1.01–1.20)
$Dose_{mean}$ (mg/day)	<0.001	0.98 (0.97–0.99)
Late AKI		
Diabetes	0.02	1.68 (1.16–1.88)
Duration of therapy (days)	0.02	1.17 (1.02–1.33)

C_{mean} mean vancomycin concentration over the first 3 days of therapy, $Dose_{mean}$, mean vancomycin daily dose over the first 3 days of therapy

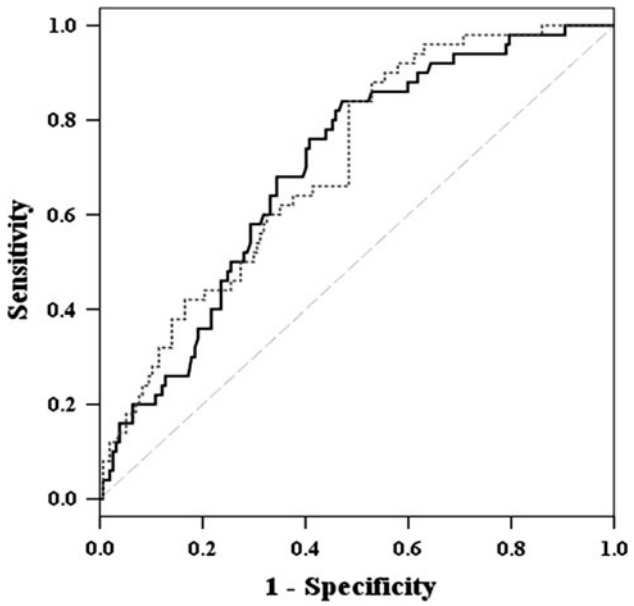

Fig. 4 Receiver operating characteristic (ROC) curves constructed to study the ability of mean vancomycin concentrations (C_{mean}, *gray dotted line*) or C_{mean} and duration of therapy (*black line*) to predict the development of acute kidney injury (AKI) during vancomycin therapy. The area under the ROC curve is 0.70 [95 % confidence interval (CI), 0.62–0.77] for C_{mean} and 0.71 (95 % CI, 0.63–0.78) for C_{mean} and duration of therapy. A $C_{mean} > 30$ μg/ml enabled the prediction of AKI during vancomycin therapy with a sensitivity of 22 %, a specificity of 90 %, a positive predictive value (PPV) of 40 %, and an negative predictive value (NPV) of 79 %

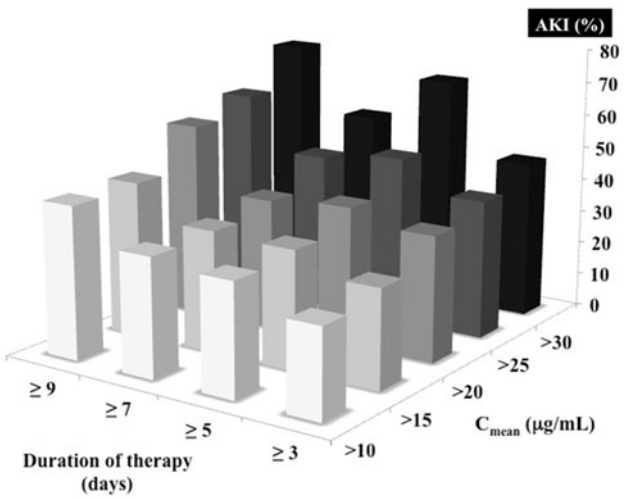

Fig. 5 Occurrence of acute kidney injury (AKI) in relation to different ranges of C_{mean} and duration of therapy

associated with the occurrence of early AKI, whereas duration of therapy and diabetes were independently associated with the occurrence of late AKI (Table 2).

Discussion

We have shown that AKI developed in one-fourth of critically ill patients treated with a continuous infusion of vancomycin. More than half the episodes of AKI occurred within 48 h of therapy. AKI was more common in more severely ill patients. As expected, the development of AKI resulted in a greater need for CRRT/HD and in higher sCr at 1 month after the initiation of therapy than in patients without AKI. Finally, C_{mean} and duration of therapy were the strongest variables for predicting AKI during vancomycin therapy, with C_{mean} being particularly associated with early AKI and duration of therapy with late AKI.

AKI is a common complication in critically ill patients, with incidence ranging from 10 to 25 % in the various cohorts, and is uniformly associated with a poor outcome [14]. Although AKI has been recognized as one of the most severe complications associated with vancomycin administration, the mechanisms, including tubular epithelial cells necrosis, oxidative and inflammatory stress, and mitochondrial damage [22, 23], have not been clearly identified. In humans, vancomycin has been reported to induce tubulo-interstitial necrosis or nephritis; moreover, the development of AKI increases if combined with other drugs, such as aminoglycosides [24, 25]. Furthermore, several prospective studies have reported that vancomycin was associated with a higher incidence of AKI than other anti-MRSA drugs, such as linezolid, tigecycline, or daptomycin [12, 26, 27].

The studies evaluating the risk of AKI during vancomycin therapy in different populations, including critically ill patients, have reported incidences ranging from 7 to 40 % (Table 3). However, our findings have some important differences when compared to previous articles. First, we did not find any relationship between daily vancomycin dose and the occurrence of AKI. Lodise et al. [8] and Jeffres et al. [10] reported that daily doses of vancomycin exceeding 4 g or 30 mg/kg were predictive of the development of AKI, especially if associated with elevated body weight and low CrCl. However, one cannot exclude that, in these studies, patients with a greater severity of illness were more likely to receive more aggressive vancomycin regimes, explaining the harmful effects of high initial doses. In our patients, early AKI patients received even lower vancomycin doses than patients without AKI, because of dose adaption to initially lower CrCl, and we observed no cases of renal dysfunction among those patients receiving doses higher than 4 g/day (data not shown).

Second, we found that C_{mean} was independently associated with the development of AKI, but only for early-onset AKI. In a retrospective analysis, Lodise et al. [28]

Table 3 Summary of the most important articles, including adult intensive care unit (ICU) patients, which evaluated the incidence of acute kidney injury (AKI) during vancomycin therapy

Reference	*n*	Type	%ICU	Age	Regimen	Definition of AKI	AKI incidence (%)	Mortality in AKI patients (%)	CRRT need	Vancomycin regimen	Vancomycin concentrations
Bosso et al. [11]	288	P	36	NA	II	Increase sCr ≥0.5 mg/l/50 %	30	NA	NA	–	C_{min} > 15 μg/ml had increased risk of AKI
Cano et al. [41]	188	R	100	58	II	Increase sCr ≥0.5 mg/l/50 %	15	33 %	NA	–	Initial C_{min} > 15 μg/ml had increased risk of AKI
Colares et al. [42]	19	R	57	51	II	50 % increase in baseline sCr	100	53	37	–	Highest C_{min} > 40 μg/ml in all patients with AKI
Hidayat et al. [29]	95	P	42	72	II	Increase sCr ≥0.5 mg/l	12	NA	NA	–	AKI occurred only if C_{min} > 15 μg/ml
Hutschala et al. [43]	149	R	100	59	II CI	Increase sCr ≥0.3 mg/l	37 27	NA	30 % 23 %	Similar daily doses between groups	Mean levels higher in CI (25 vs. 17 μg/ml)
Jeffres et al. [10]	94	R	NA[a]	59	II	Increase sCr ≥0.5 mg/l/50 %	43	NA	0 %	–	C_{min} > 15 μg/ml had increased risk of AKI
Lodise et al. [28]	166	R	36	56	II	Increase sCr ≥0.5 mg/l/50 %	13	NA	NA	–	Initial C_{min} was associated with AKI development
Lodise et al. [8]	246	R	41	58	II	Increase sCr ≥0.5 mg/l/50 %	12	NA	0 %	>4 g/day was associated with increased AKI	–
Minejima et al. [30]	227	P	33	70	II	Increase sCr ≥0.3 mg/l	19	19 %	0 %	Lower initial dose in AKI group	Vancomycin levels were not associated with AKI
Pritchard et al. [9]	129	R	NA[a]	61	II	Increase sCr ≥0.5 mg/l/50 %	16	NA	NA	Higher initial dose in patients with AKI	Higher mean C_{min} in patients with AKI
Shen et al. [35]	33	R	30	71	II	1.5-fold increase in sCr	45	40 %	6 %	–	–
Spapen et al. [18]	129	R	100	67	CI	Increase sCr ≥0.3 mg/l	29	53 %	0 %	–	C_{max} was associated with AKI

R retrospective, *P* prospective, *%ICU* percentage of ICU patients included in the study, *II* intermittent infusion, *CI* continuous infusion, *sCr* serum creatinine, C_{min} trough concentration, C_{max} maximal drug concentration during therapy, *CRRT* continuous renal replacement therapy

[a] ICU patients were included but how many was not specifically reported

reported that each increase in the initial trough drug concentration was associated with an OR of 1.13 for AKI occurrence. In other studies, vancomycin trough levels greater than 15–20 μg/ml were also identified as a significant predictor of AKI during therapy [8–10, 28, 29]. In contrast, Minejima et al. [30] found that the strongest determinants of AKI included a prior episode of AKI, a history of malignancy, and baseline renal function, whereas vancomycin trough levels were not significantly related to the development of AKI. As vancomycin is almost entirely eliminated by the kidneys, drug clearance varies linearly with CrCl [6]. As such, an alteration in renal function from any cause will increase vancomycin concentrations and it is very difficult to evaluate whether elevated drug levels are responsible for renal damage or only represent a marker of decreased glomerular filtration rate (GFR). We found that patients who developed AKI early were more severely ill and had a worse renal function at baseline; renal

deterioration was related more to the underlying sepsis, as suggested by the predictive role of bacteremia on early AKI, rather than to the drug itself. Few studies have evaluated the occurrence of early AKI during vancomycin therapy; Lodise et al. [8] found that one-sixth of patients developing renal dysfunction during vancomycin therapy had early AKI and that these patients also had higher severity scores and risk of renal injury.

Third, the duration of therapy was an independent predictor of AKI, especially for the late onset of renal dysfunction. These data are in line with previous studies, which also reported, for intermittent infusion and non-ICU populations, that the onset of AKI ranged from 4 to 8 days from the start of therapy and the duration of drug exposure could influence the development of AKI [8, 28, 31]. As we also found that diabetes was independently associated with late AKI, it is possible that pre-existing renal dysfunction, such as in chronic diabetic nephropathy, could be a predisposing factor for AKI when prolonged administration of vancomycin is used. Spapen et al. [18] also found that patients with AKI during vancomycin therapy were more likely to be diabetic than patients without AKI (79 vs. 54 %; $p = 0.01$).

Fourth, the concomitant administration of nephrotoxic agents did not contribute to the development of AKI in the multivariable analysis. This is in contrast with other studies on vancomycin-treated patients, which showed that aminoglycosides [8, 32, 33] or loop diuretics [10, 33] were associated with AKI, especially if drug trough concentrations exceeded 15 μg/ml. It is possible that the influence of concomitant nephrotoxic agents on AKI in our cohort was blunted by the high severity of illness [8, 10, 33].

Fifth, the high incidence of AKI we observed, when compared to previous studies, was probably related to the criteria we used, which considered an increase of at least 0.3 mg/dl of sCr from the initial value as the cut-off to define renal dysfunction [14, 18, 30]. Previous studies often used a ≥50 % change in sCr or CrCl or an increase in sCr of at least 0.5 mg/dl from baseline values to identify AKI (Table 3). If we had used this latter criterion, only 39 of our patients (19 %) would have been defined as developing AKI (data not shown). The use of more strict criteria to define AKI [4] may potentially improve the care of these patients by facilitating early detection of renal dysfunction [30] and, hence, earlier therapy. Definitions need to be considered when comparing the occurrence of AKI among different studies.

Finally, a continuous infusion of vancomycin may result in less AKI than standard vancomycin administration [17], but most of the studies have only considered standard regimes. One recent retrospective study on 129 critically ill patients receiving a continuous infusion of vancomycin reported a 29 % incidence of AKI; in this study, serum vancomycin concentrations above 30 mg/ml were independently associated with the development of AKI [18]. However, this study took into consideration only the highest value of vancomycin concentrations over the period of treatment, which does not take into account the exposure of the kidney to toxic levels of vancomycin over time. In addition, no data on the long-term consequences of AKI were reported in this population. We observed that, among survivors, patients who developed AKI had a higher sCr at 1 month after the onset of vancomycin therapy, despite similar sCr values on admission. Previous studies have reported conflicting results; in three studies, resolution of the nephrotoxicity was seen in 70–80 % of patients and none of these patients required renal replacement therapy as a consequence of AKI [8, 10, 30]. However, in two other studies, CRRT was used in 6 % of patients receiving vancomycin and with abnormal renal function on ICU admission [34, 35]. The implementation of new antimicrobial agents with less nephrotoxicity (i.e., shift from vancomycin to linezolid) in critically ill surgical patients has been associated with a reduced need for CRRT/HD [36]. It remains unclear as to whether the shift to less nephrotoxic agents, such as linezolid [34], in these cases would also allow renal recovery. Interestingly, Teng et al. [37] reported that vancomycin was continued in 10 patients developing AKI, with 7 of the 10 patients showing no further decline in renal function and five of them eventually returning to baseline sCr at discharge.

This study has some limitations. First, continuous infusion of vancomycin regimens have been validated in patients with severe MRSA infections; however, several studies have suggested the need for higher doses in ICU patients [38, 39] and the effects of such regimens on AKI occurrence need to be further studied. Second, we specifically focused on continuous infusion of vancomycin, but it remains unclear as to whether the method of administration of vancomycin (intermittent vs. continuous infusion) is a major determinant for the development of AKI. Studies that have compared these two strategies have yielded conflicting results and current guidelines advise against the administration of vancomycin in continuous infusion, because no clinical benefit over intermittent dosing has been demonstrated and this strategy may not adequately optimize the antibacterial properties of the drug [4]. Third, a control group with the same disease severity would have been necessary in order to assess the real impact of vancomycin on renal function in this setting. In one study, AKI occurred in 17 % of patients receiving vancomycin and in 5 % of control patients [40]. Data from studies comparing vancomycin to other drugs suggest a higher incidence of AKI with vancomycin [12]. However, vancomycin was largely underdosed in the early phase of therapy and these studies analyzed only elderly subjects or did not focus on

ICU patients, making it difficult to extrapolate these conclusions to a critically ill population. Fourth, sCr is not a sensitive biomarker for rapidly detecting mild changes in renal function and the use of urinary and/or serum biomarkers of AKI may help to improve the accuracy of AKI diagnosis in the future. Fifth, we did not report other adverse effects associated with vancomycin administration, such as ototoxicity, neutropenia, phlebitis, or toxic epidermal necrolysis, although their incidence is very rare [44, 45]. Fifth, we recorded the use of other potential nephrotoxics, but no information regarding the length of exposure for each of these agents was available. Finally, our study was retrospective and we may have underestimated or misclassified some important determinants of AKI in this setting, and the temporal relationship between drug concentrations elevation and the occurrence of AKI could not be precisely assessed. Also, considering the local expertise in using continuous infusion of vancomycin over a number of years and the monocentric data collection, we could not evaluate the extent to which our results could be generalized to other ICUs.

Conclusions

Using a continuous infusion vancomycin regimen, acute kidney injury (AKI) occurred in one-fourth of critically ill patients and was associated with an increased need for continuous renal replacement therapy (CRRT) or conventional hemodialysis (HD) and altered residual renal function at 1 month. Early AKI was associated with the occurrence of bacteremia and higher mean drug concentrations over the first 3 days of therapy, but was likely the result of sepsis and of a more severe clinical condition than direct drug toxicity. Late AKI was associated with the duration of drug exposure and may be enhanced by the presence of concomitant diseases responsible for chronic renal dysfunction, such as diabetes.

Acknowledgments We thank Mr. Hassane Njimi for his help with the statistical analysis. The study was supported by institutional funds only. It was not supported by any grants.

Conflict of interest The authors declare that they have no competing interests.

References

1. Griffin AT, Peyrani P, Wiemken TL, Ramirez JA, Arnold FW. Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia. Infection. 2013;41:517–23.
2. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med. 2004; 30:589–96.
3. Hanberger H, Walther S, Leone M, Barie PS, Rello J, Lipman J, et al. Increased mortality associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the intensive care unit: results from the EPIC II study. Int J Antimicrob Agents. 2011;38:331–5.
4. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC Jr, Craig WA, Billeter M, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2009;29:1275–9.
5. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis. 2012;54:755–71.
6. Gupta A, Biyani M, Khaira A. Vancomycin nephrotoxicity: myths and facts. Neth J Med. 2011;69:379–83.
7. Hazlewood KA, Brouse SD, Pitcher WD, Hall RG. Vancomycin-associated nephrotoxicity: grave concern or death by character assassination? Am J Med. 2010;123:182.e1–7.
8. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother. 2008;52:1330–6.
9. Pritchard L, Baker C, Leggett J, Sehdev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. Am J Med. 2010;123:1143–9.
10. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther. 2007;29:1107–15.
11. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrob Agents Chemother. 2011;55:5475–9.
12. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012;54:621–9.
13. Ocampos-Martinez E, Penaccini L, Scolletta S, Abdelhadii A, Devigili A, Cianferoni S, et al. Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients. Int J Antimicrob Agents. 2012;39:332–7.
14. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
15. Marsot A, Boulamery A, Bruguerolle B, Simon N. Vancomycin: a review of population pharmacokinetic analyses. Clin Pharmacokinet. 2012;51:1–13.
16. Wysocki M, Delatour F, Faurisson F, Rauss A, Pean Y, Misset B, et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother. 2001;45:2460–7.
17. Cataldo MA, Tacconelli E, Grilli E, Pea F, Petrosillo N. Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother. 2012;67:17–24.
18. Spapen HD, Janssen van Doorn K, Diltoer M, Verbrugghe W, Jacobs R, Dobbeleir N, et al. Retrospective evaluation of possible renal toxicity associated with continuous infusion of vancomycin in critically ill patients. Ann Intensive Care. 2011;1:26.
19. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250–6.

20. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–29.
21. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.
22. Nishino Y, Takemura S, Minamiyama Y, Hirohashi K, Ogino T, Inoue M, et al. Targeting superoxide dismutase to renal proximal tubule cells attenuates vancomycin-induced nephrotoxicity in rats. Free Radic Res. 2003;37:373–9.
23. Dieterich C, Puey A, Lin S, Swezey R, Furimsky A, Fairchild D, et al. Gene expression analysis reveals new possible mechanisms of vancomycin-induced nephrotoxicity and identifies gene markers candidates. Toxicol Sci. 2009;107:258–69.
24. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int J Antimicrob Agents. 2011;37:95–101.
25. Wu CY, Wang JS, Chiou YH, Chen CY, Su YT. Biopsy proven acute tubular necrosis associated with vancomycin in a child: case report and literature review. Ren Fail. 2007;29:1059–61.
26. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E; Tigecycline 300 cSSSI Study Group; Tigecycline 305 cSSSI Study Group. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin–aztreonam. Clin Infect Dis. 2005;41:S341–53.
27. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med. 2006;355:653–65.
28. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration–time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis. 2009;49:507–14.
29. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med. 2006;166:2138–44.
30. Minejima E, Choi J, Beringer P, Lou M, Tse E, Wong-Beringer A. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother. 2011;55:3278–83.
31. Zimmermann AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy. 1995;15:85–91.
32. Farber BF, Moellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob Agents Chemother. 1983;23:138–41.
33. Hermsen ED, Hanson M, Sankaranarayanan J, Stoner JA, Florescu MC, Rupp ME. Clinical outcomes and nephrotoxicity associated with vancomycin trough concentrations during treatment of deep-seated infections. Expert Opin Drug Saf. 2010;9:9–14.
34. Rodriguez Colomo O, Álvarez Lerma F, González Pérez MI, Sirvent JM, García Simón M; Study Group of Infection in Critical Patients. Impact of administration of vancomycin or linezolid to critically ill patients with impaired renal function. Eur J Clin Microbiol Infect Dis. 2011;30:635–43.
35. Shen WC, Chiang YC, Chen HY, Chen TH, Yu FL, Tang CH, et al. Nephrotoxicity of vancomycin in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. Nephrology (Carlton). 2011;16:697–703.
36. Eichhorn ME, Wolf H, Küchenhoff H, Joka M, Jauch KW, Hartl WH. Secular trends in severe renal failure associated with the use of new antimicrobial agents in critically ill surgical patients. Eur J Clin Microbiol Infect Dis. 2007;26:395–402.
37. Teng CB, Rezai K, Itokazu GS, Xamplas RC, Glowacki RC, Rodvold KA, et al. Continuation of high-dose vancomycin despite nephrotoxicity. Antimicrob Agents Chemother. 2012;56:3470–1.
38. Jeurissen A, Sluyts I, Rutsaert R. A higher dose of vancomycin in continuous infusion is needed in critically ill patients. Int J Antimicrob Agents. 2011;37:75–7.
39. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother. 2011;55:2704–9.
40. Downs NJ, Neihart RE, Dolezal JM, Hodges GR. Mild nephrotoxicity associated with vancomycin use. Arch Intern Med. 1989;149:1777–81.
41. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. Clin Ther. 2012;34:149–57.
42. Colares VS, Oliveira RB, Abdulkader RC. Nephrotoxicity of vancomycin in patients with normal serum creatinine. Nephrol Dial Transpl. 2006;21:3608.
43. Hutschala D, Kinstner C, Skhirdladze K, Thalhammer F, Müller M, Tschernko E. Influence of vancomycin on renal function in critically ill patients after cardiac surgery: continuous versus intermittent infusion. Anesthesiology. 2009;111:356–65.
44. Bossé D, Lemire C, Ruel J, Cantin AM, Ménard F, Valiquette L. Severe anaphylaxis caused by orally administered vancomycin to a patient with *Clostridium difficile* infection. Infection. 2013;41:579–82.
45. Rocha JL, Kondo W, Baptista MI, Da Cunha CA, Martins LT. Uncommon vancomycin-induced side effects. Braz J Infect Dis. 2002;6:196–200.